REMARKS

Upon entry of this amendment, claims 1-30 and 43-63 are pending in the application. Claims 1, 2, 5-7, 11, 15-18, 20-22, 24, and 30 have been amended. Support for these amendments can be found throughout the specification as-filed, *e.g.* at page 3, lines 7-15 of the specification; and page 13, line 26 through page 14, line 4. New claims 43-63 have been added. Support for the new claims can be found throughout the specification as filed and in original claims 2-21. In support of the remarks and arguments stated *infra*, Applicants have submitted herewith the Declaration of Dr. Nir Dotan under 37 C.F.R. §1.132 ("Dotan Declaration"). No new matter has been added.

Rejections under 35 USC § 112, first paragraph

Claims 1-10, 12-24, and 26-30 are rejected for lack of enablement (*See* Office Action at pages 2-3). The rejection is traversed as it applies to the claims as amended.

Claim 1, from which claims 2-10, and 12-21 depend, has been amended to require identification of an anti-GlcNAc (β 1-4) GlcNAc (β) antibody, wherein the identification of elevated levels of the antibody in the test sample relative to a control sample indicates the subject has Crohn's disease. Claim 22, from which claims 23, 24, and 26-29 depend, has been amended to require identification of an anti-Glc (β 1-3) Glc (β) antibody, wherein the identification of elevated levels of the antibody in the test sample relative to a control sample indicates the subject has Crohn's disease. Claim 30 has been amended to require identification of ANCA or IgG anti-Glc (β 1-3) Glc (β) and IgG ASCA or IgA ASCA.

Applicants submit that the amended claims are fully enabled by the as-filed specification. Specifically, Example 1 illustrates that increased levels of both anti-GlcNAc (β 1-4) GlcNAc (β)

antibody and anti-Glc (β 1-3) Glc (β) antibody are detected in the serum of patients with Crohn's disease as compared to the normal population and individuals with other digestive diseases. (*See* Specification at Example 1 and Tables 2 and 3.) Moreover, Figure 1 shows that levels of anti Glc (β 1-3) Glc (β) can differentiate between individuals with CD and individuals with other digestive diseases. Applicants submit that this rejection for lack of enablement has been overcome and should be withdrawn.

According to the Examiner, claim 30 is rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. (*See* Office Action at page 3.) Specifically, the Examiner has stated that the specification does not provide support for diagnosis of inflammatory bowel disease when ANCA is absent.

Claim 30 has been amended to require the presence of ANCA for the diagnosis of inflammatory bowel disease. Applicants submit that this rejection has been overcome and should be withdrawn.

Rejections under 35 USC § 112, second paragraph

Claims 1-30 are rejected as indefinite, on various grounds (*See* Office Action at pages 3-4). The claims have been amended to address the rejections.

Rejections under 35 USC § 101

Claims 22-29 are provisionally rejected for statutory double-patenting in view of claims 22-29 of USSN 10/843,033 (*See* Office Action at page 4). Applicants will address this rejection upon the indication of allowable subject matter in either application.

Rejections under 35 USC § 102(b)

Claims 1-8, 11-15, 17-19, and 21-28 are rejected as anticipated by Main *et al.* BMJ 297:1105, 1988 ("Main") in light of Applicants' disclosure, Sendid *et al.*, Clin. Diagn. Lab. Immunol. 3:219, 1996 ("Sendid"), and/or Wakshull *et al.*, US Patent No. 6,294,321 ("Wakshull"). The rejection is traversed to the extent it is applied to the claims as amended.

Claim 1, from which claims 2-8, 11-15, 17-19, and 21 depend, has been amended to require identification of an anti-GlcNAc (β 1-4) GlcNAc (β) antibody, wherein the identification of elevated levels of the antibody in the test sample relative to a control sample indicates the subject has Crohn's disease. Claim 22, from which claims 23, 24, and 26-29 depend, has been amended to require identification of an anti-Glc (β 1-3) Glc (β) antibody, wherein the identification of elevated levels of the antibody in the test sample relative to a control sample indicates the subject has Crohn's disease.

Main does not describe or suggest the claimed methods. According to the Examiner, Main describes detection of IgG and IgA antibodies to a crude extract of *Saccharomyces cerevisiae* (ASCA) in Crohn's disease (CD), but not ulcerative colitis (UC), patient samples (*See* January 5, 2007 Office Action at page 6). However, there is no teaching or suggestion in Main of a method that requires specifically identifying the particular anti-glycan antibodies recited in the

claims. Specifically, there is no teaching or suggestion in Main of a method that requires the identification of an anti-GlcNAc (β 1-4) GlcNAc (β) antibody, as required by claim 1, or an anti-Glc (β 1-3) Glc (β) antibody, as required by claim 22, wherein the identification of elevated levels of the antibody in the test sample relative to a control sample indicates the subject has Crohn's disease.

As new claims 43-61 and 63 depend from claim 22, they necessarily incorporate all of the limitations of that claim. Similarly, as new claim 62 depends from claim 1, it necessarily incorporates all of the limitations of that claim.

Claims 1-8, 11-20, and 22-28 are rejected as anticipated by Sendid in light of Applicants' disclosure and/or Wakshull. According to the Examiner, Sendid detected antibodies to *Saccharomyces cerevisiae* (ASCA) cells in the circulation of Crohn's disease (CD), but not ulcerative colitis (UC) patient samples by immunofluorescence (*See* January 5, 2007 Office Action at page 6). The Examiner states that Sendid inherently detected antibodies to the glycan epitopes. However, the data presented in Sendid do not support the conclusion that antibodies in Crohn's disease patients always detect epitopes in *Saccharomyces cerevisiae* strains, which can differ in their outer membrane glycan antigens epitopes. (*See* Dotan Declaration at ¶11.) According to Sendid, not all *Saccharomyces cerevisiae* strains examined reacted with sera from CD patients. Although phosphopeptidomannan exists in the cell wall of all *Saccharomyces cerevisiae*, only *Saccharomyces cerevisiae* strain Su1 and *Saccharomyces cerevisia* Sd are reactive to CD sera. (*See* Dotan Declaration at ¶11.) Sendid reported that antibodies to whole cells of *Saccharomyces cerevisiae* BM156, *Saccharomyces cerevisiae* BM151, and *Saccharomyces cerevisiae* CBS1315 were not specific to CD. (*See* Sendid at Table 1, page 221.)

Furthermore, recent data suggest that antigens triggering elevated levels of ALCA in CD patients are not related to *Saccharomyces cerevisiae*, but rather originated from exposure to *Candida albicans* cells (exists in natural human intestine flora) crossing the leaky bowel of CD patients. (*See* Dotan Declaration at ¶13 and Figures 5-6.)

Although Wakshull is cited for describing β (1-3)-glucans and mannans as components of yeast cell cells, it does not discuss CD, nor does it report diagnosing CD using antibodies to defined glycans. Wakshull reports the detection of soluble β (1-3)-glucans in the blood of patients suffering from invasive fungal infections. Such detection was performed by anti β (1-3)-glucan monoclonal antibody coupled to a solid phase as a capture molecule. In contrast, the claimed methods require detecting the level of autoantibodies in serum of CD patients. Such detection is performed by immobilized β (1-3)-glucans coupled to solid phase as a capture molecule. In addition, Wakshull is apparently cited for reporting that a monoclonal antibody that recognizes a β (1-3)-glucan can cross react with one of its sub fragments, *i.e.*, laminaribioside. However, it does not follow that if polyclonal autoantibodies to polysaccharide exist in sera of CD patients and are specific to CD, then antibodies to a particular sub-fragment will exist and will be specific for the same clinical condition. (*See* Dotan Declaration at ¶12.) One cannot predict in the absence of experimentation which sub fragment of a glycan epitope will be exposed on the surface of the polysaccharide, how many of each sub fragment exists, or whether the glycan sub fragment will trigger an immune response to this specific epitope and at what level. (*See* Dotan Declaration at ¶12.1.) Results demonstrate the unpredictable nature and lack of correlation between antibody reactivity to polysaccharides and to defined fragments thereof. (*See* Dotan Declaration at ¶12.2-12.3 and Figures 1-2.) Therefore, the claimed invention

represents a significant advance in diagnosing CD that was not discussed or suggested in either Sendid or Wakshull.

Finally, there is no teaching or suggestion in Sendid or Wakshull of a method that requires specifically identifying the particular anti-glycan antibodies recited in the claims. Specifically, there is no teaching or suggestion in Sendid or Wakshull of a method that requires the identification of an anti-GlcNAc (β 1-4) GlcNAc (β) antibody, as required by claim 1, or an anti-Glc (β 1-3) Glc (β) antibody, as required by claim 22, wherein the identification of elevated levels of the antibody in the test sample relative to a control sample indicates the subject has Crohn's disease.

As new claims 43-61 and 63 depend from claim 22, they necessarily incorporate all of the limitations of that claim. Similarly, as new claim 62 depends from claim 1, it necessarily incorporates all of the limitations of that claim.

Claims 22, 24 and 26-30 are rejected as anticipated by Quinton *et al.*, Gut 42:788, 1998 ("Quinton") in light of Walsh *et al.*, US Patent No. 6,218,129 ("Walsh"). According to the Examiner, Quinton discriminated ulcerative colitis (UC) from Crohn's disease (CD) by determinations of anti-neutrophil cytoplasmic auto-antibodies in the serum of patients and controls (*See* January 5, 2007 Office Action at page 6). The Examiner states that Quinton detected at least IgG and IgA ASCA. However, there is no teaching or suggestion in Quinton of a method that requires specifically identifying the particular anti-glycan antibodies recited in the claims. Specifically, there is no teaching or suggestion in Quinton of a method that requires the identification of an anti-GlcNAc (β 1-4) GlcNAc (β) antibody, as required by claim 1, or an anti-Glc (β 1-3) Glc (β) antibody, as required by claim 22, wherein the identification of elevated

levels of the antibody in the test sample relative to a control sample indicates the subject has Crohn's disease.

As new claims 43-61 and 63 depend from claim 22, they necessarily incorporate all of the limitations of that claim. Similarly, as new claim 62 depends from claim 1, it necessarily incorporates all of the limitations of that claim.

Applicants request reconsideration and withdrawal of the rejections for anticipation.

Rejections for Obviousness-type Double Patenting

Claims 1-21 and 30 are provisionally rejected for obviousness-type double patenting in view of claims 1-21 and 30-42 of USSN 10/843,033 (*See* Office Action at page 6). Applicants will address this rejection upon the indication of allowable subject matter in either application.

Claims 1-30 are provisionally rejected for obviousness-type double patenting in view of claims 1-3, 7-12, and 18-29 of USSN 11/351,185 (*See* Office Action at page 6). Applicants will address this rejection upon the indication of allowable subject matter in either application.

Claims 1-30 are provisionally rejected for obviousness-type double patenting in view of claims 1-3, 7-12, and 18-29 of USSN 11/364,964 (*See* Office Action at page 6). Applicants will address this rejection upon the indication of allowable subject matter in either application.

On the basis of the foregoing amendments and remarks, Applicants submit the pending claims are in condition for allowance. Such action is respectfully requested. The Commissioner is authorized to charge any fees that may be due to Deposit Account No. 50-0311, Reference No. 25681-502 P.

Respectfully submitted,

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